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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,797	VISVADER ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *2,4,6,10-17,21 and 24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7-9,18-20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/4/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1, 3, 18-20, 22-23 and 5-9 in part) with species of mammary cell and hybridoma 16H2 in the reply filed on 11/252005 is acknowledged.

The traversal is on the ground(s) that Groups I-VIII are merely different aspects of a single invention and are not independent. In response to the argument, the groups I-VIII are patentably distinct inventions, which have been discussed in the prior Office action (requirement for Restriction/election, 5/23/05).

Applicants also request examination of the Group I, II and IV together. As discussed in the prior Office action (5/23/05). Group I, II, and IV are distinct because Group I (claims 1, 3, 18-20, 22-23 and 5-9 in part) is drawn to a method for detecting an aberrant cell with an **immunointeractive molecule or antibody** specific for LMO4, which is a method to detect levels of LMO4 protein to determine the an aberrant cells. Group II (2, 4, 24-29 and 5-9 in part) is drawn to a method for detecting or monitoring a aberrant cell by screening the level of **LMO4 transcription**, which is a method to detect expression of LMO4 by determining the levels of mRNA. Group IV is drawn to a method for detecting a neoplastic cell **in a patient** comprising **introducing a patient** with antibody, which is an in vivo method to detecting neoplastic cells. All the methods are distinct because they have different method steps and use different materials and may have different patient population or biological samples. Searching all three methods are not co-extensive in non-patent literature and US patent database, which would impose a serious search burden.

Applicants also argue that reliance on the supposed classification of the groups of claims does not establish independence and distinctness and classification is instead an aid in finding and searching for patents. Office agrees with Applicants in this aspect that the classification is merely an aid in finding and searching for patents or a patent application. Therefore, the restriction requirement of prior office action in this case is not based on the classification of each group instead based on the inventions. Invention groups I-VIII have different in method objectives, method steps, and the reagents used. The instant specification does not disclose these methods would be used together. In the biotechnology field,

the patentability of a patent application significantly depend on the results of key word search or/and sequence search in US and international patent databases and non-patent literatures. Since all groups in this application have separate use and operation, the literature search and sequence database search, particularly relevant in this art, are not co-extensive and clearly different searches and issues are involved in the examination of each group. Therefore, searching all or even two groups together in those databases would impose a serious search burden. For the reasons above, the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made **FINAL**.

Claims 1-39 are pending, Claims 2, 4, 6, 10-17, 21, 24-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. After review and reconsideration of the elected species in light of the prior art, the species of hybridoma 20F8 is joined to the species of hybridoma 16H2 for examination at this time. Claims 1, 3, 5, 7-9,18, 19-20, 22-23 with species mammary cell are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 2/4/05 are/is considered by the examiner and initialed copy of the PTO-1449 is enclosed.

Priority

1. Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No, PCT/AU02/01246, under 35 U.S.C. 119(a)-(d) or (f), a claim for such foreign priority must be timely made in this application. To satisfy the requirement of 37 CFR 1.55(a)(2) for a certified copy of the foreign application, applicant may simply identify the application containing the certified copy.

2. Acknowledgment is made of applicant's claim for foreign priority also based on an application filed in Australia on 09/12/2001. It is noted, however, that applicant has not filed a certified copy of the PR7618/01 application as required by 35 U.S.C. 119(b). Therefore, for the purposes of examining this

application, the examiner has established the effective priority dated of September 12, 2002, the filing dated of the instant application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the **second paragraph of 35 U.S.C. 112**:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 23 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 23 are indefinite because the term "derived from" and "derived parts" of" in the claims are not clear. It is not clear that the terms "derived from" or "derived part" means "obtained from" or "obtained parts". Therefore, the metes and bounds of the claims cannot be determined.

2. The following is a quotation of the **first paragraph of 35 U.S.C. 112:**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Drawn to deposit of hybridoma 16H2 and 20F8:

Claims 18, 20, and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of a hybridoma cell line hybridoma 16H2 or hybridoma 20F8. It is not clear that the antibody secreted by hybridoma 16H2 or

hybridoma 20F8 is known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody secreted by hybridoma 16H2 or hybridoma 20F8, a suitable deposit of hybridoma 16H2 or hybridoma 20F8 for patent purposes, evidence of public availability of the claimed method using antibody secreted by hybridoma 16H2 or hybridoma 20F8 or evidence of the reproducibility without undue experimentation of the claimed invention, is required.

Applicant's referral to the deposit hybridoma cell line as 16H2 or hybridoma 20F8 on page 29, paragraph 4 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the hybridoma16H2 or hybridoma 20F8, deposited at ATCC deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit hybridoma cell line 16H2 or hybridoma 20F8 has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit of hybridoma 16H2 or hybridoma 20F8 is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Drawn to enablement: forming a complex of LMO/immunointeractive molecule or antibody mutant or variant thereof, derivative, analogue mutant thereof:

Claims 1, 3, 5, 7-9, 18, 20, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The set of claims are broadly drawn to a method for detecting an aberrant cell or a predisposition to the development of mammary cells in a subject by screening the levels of complex of forming LMO4 or fragment, variant or derivative thereof with immunointeractive molecule, derivative, analogue or mutant thereof or with antibodies secreted hybridoma16H2 or hybridoma 20F8 or mutant or variant thereof.

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. The method objective of claims is a method for detecting an aberrant cell by formation of complex of LMO4 or its variants thereof with immunointeractive molecule, derivatives thereof or with antibodies secreted hybridoma16H2 or hybridoma 20F8 or its variant thereof. Thus, it would be expected that one of skill in the art would be able to detecting an aberrant cell by determining the LMO4-antibody complex, or LMO4-immunointeractive molecule complex formation in a mammary cell without undue experimentation by using the claimed method.

First, The specification on page 21, last paragraph, teaches that the "immunointeractive molecule" is any molecule having specificity and binding affinity for LM04 or its antigenic parts or its homologues or derivatives. Although the preferred immmunointeractive molecule is an immunglobulin

molecule, the present invention extends to other immunointeractive molecules such as antibody fragments, single chain antibodies, deimmunized including humanized antibodies and T-cell associated antigen-binding molecules (TABMs). The specification also states that the subject immunointeractive molecule may be limited, bound or otherwise associated to any other proteinaceous or non-proteinaceous molecule or cell. However, the specification neither disclose functional or structural attributes of an immunointeractive molecule other than antibodies, nor any other immunointeractive molecule other than an antibody, which are immunoreactive to LMO4 and forming a complex with LMO4. The specification does not provide any method to detect LMO4 in a mammary cell or a working example, which enables immunointeractive molecule other than an antibody to detect LMO4 in a mammal cell. Therefore, one skilled in the art would not know how to use the claimed immunointeractive molecule other than an antibody based on the teachings in the prior art or instant specification.

Secondly, The specification, on page 32, paragraphs 3, states that the invention extends to mutants, analogues, and derivative of the subject antibodies but which still retain specificity for LMO4. The specification further states on paragraph 4, that the terms "mutant" or "derivative" include one or more amino acid substitutions, additions and/or deletions. However, the specification does not teach any working example, which enables the composition in the claims that specifically bind to LMO4 protein or any LMO4 fragment, variant or derivative thereof. The specification does not teach any working example having identified a complex formed by LMO4 protein or a fragment, derivative or variant with an antibody secreted hybridoma16H2 or hybridoma 20F8 or mutant or variant thereof. The specification does not provide any teaching on antibody secreted by hybridoma 16H2 or 20F8, mutant, variant thereof which could form a complex with LMO4 protein or its variant. Thus, the instant specification fails to disclose the necessary parameters for using the method, which would lead to the detection of aberrant cell by screening the level of immunointerative molecule-LMO4 complex comprising fragment, mutant, variant, analogy thereof, or antibody-LMO4 complex comprising mutant, derivative, fragment variant thereof.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the

protein (Burgess et al, Journal of Cell biology, Vol 111, p2129-2138, 1990). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Therefore, an undue experimentation is required to test any of claimed composition having a modulating function for any protein, which is even a minor different in its structure or sequence from a known protein.

Since the specification does not provide compositions used in the claims and not provide claimed method, since the specification does not provide any guidance for screening levels of the LMO4 complex using LMO4 or its variants, immunointeractive molecule, derivatives thereof or with antibodies secreted hybridoma16H2 or 20F8 or its variant thereof as discussed above, one skilled in the art would not know how to use the claimed method to detecting aberrant cells in a biological sample on the basis of teachings in the prior art or instant specification.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to detecting aberrant cells by the LMO4 complex formation with immunointeractive molecule, derivatives thereof or with antibodies secreted hybridoma16H2 or 20F8 or its variant thereof, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention.

Drawn to enablement- at least one of the CDRs of the varialb domain of deimmunized LMO4 antibody:

Claims1, 3, 18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claims1, 3, 18 and 23 are drawn to a method of for detecting an aberrant cell or a predisposition to the development of an aberrant cell in a subject by screening the levels of complex of forming LMO4 with an deimmunized antibody wherein at least one of the CDRs of the variable domain of the antibody derived from the monoclonal antibody to LMO4. Thus, the claims encompass using a monoclonal antibody, which does not contain a full set of 6 CDRs.

The specification on para 20, PGpub 20050048528, states "invention contemplates a deimmunized antibody molecule having specificity for an epitope recognized by a monoclonal antibody to LMO4 wherein at least one of the CDRs of the variable domain of said deimmunized antibody is derived from the said monoclonal antibody to LMO4 and the remaining immunoglobulin-derived parts of the deimmunized antibody molecule are derived from an immunoglobulin or an analogue thereof from the host for which the antibody is to be deimmunized". However, the specification does not provide any working example or any evidence to enable claimed antibody having at least one of the CDRs specifically binding to LMO4 antigen.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al., (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al., teach that the

alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that deimmunized antibody, thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using a deimmunized antibody, containing fewer than 6 CDRs, resulting in the antibody that retains the antigen specificity of the parental non-human antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of using a deimmunized antibody containing at least one of the CDRs. Undue experimentation would be required to use the invention commensurate with the scope of the claims from the written disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 5, 7-9, 18 -20, 22-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Visvader et al., (PNAS, vol 98, page 14452-14457, Dec 2001).

Visvader et al., disclose a method of detecting breast cancer cells, an aberrant mammary epithelia cell, by overexpression of LMO4 (page 14453, col 2, para 2). Visvader et al., disclose that LMO4 protein is detected by immunohistochemistry (formatting a complex of LMO4 protein and rat anti-LMO4 antibody, page 14453, col 1, page 3 and figure 5). Visvader et al., further disclose that 60 tumors were analyzed, overexpression of LMO4 was observed in 62% of tumors (page 14453, col 2, lines 8 from bottom).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

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SHEELA [illegible]
PRIMARY [illegible]INER